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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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Flehr Hohback Test Albritton & Herbert LLP
Four Embarcadero Center
Suite 3400
San Francisco, CA 94111-4187

EXAMINER
STRZELECKA, TERESA E

ART UNIT	PAPER NUMBER
1637	21

DATE MAILED: 05/02/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/513,362	CHEE ET AL.	
	Examiner	Art Unit	
	Teresa E Strzelecka	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 February 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-30* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Continued Prosecution Application

1. The request filed on February 20, 2003 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 09/513,362 is acceptable and a CPA has been established. An action on the CPA follows.

2. Claims 1-30 were previously pending. Applicants amended claims 1, 4, 10 and 18.

3. In a summary statement on page 5, Applicants state that new claims 31 and 32 were added, but these claims were not present in the amendment. Therefore only claims 1-30 are pending and will be examined.

Response to Arguments

4. In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, Navot et al. teach pyrosequencing of nucleic acids which may be attached to microbeads in an electrophoresis-free system, and attachment to the solid support provides confinement to the sample (col. 15, lines 1-14), and Walt et al. teach microbeads with attached nucleic acids, distributed randomly on the surface of the fiber optic bundle, creating an microbead array (col. 3, lines 35-45; col. 4, lines 35-38; col. 8, lines 15-19; col. 9, lines 41-67; col. 10, lines 1-47). Both references teach microbeads, and Walt et al. teaches an efficient and inexpensive way of creating an array (col. 4, lines 53-58). Therefore, provided with the teachings of Navot et al. and Walt et al., a skilled artisan

would be motivated to use the microbead array of Walt et al. to detect the microbead sequencing reactions of Navot et al. The rejections are maintained.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 3, 4, 5, 11, 12 and 25-27 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claims 3, 4 and 5 recite the limitation "said....sequencing primer" in lines 1, 4 and 2, respectively. There is insufficient antecedent basis for this limitation in the claims. Claim 1, from which these claims depend, contains limitations "first sequence primer" and "second sequence primer".

B) Claims 11 and 12 recite the limitation "said capture probe" in line1. There is insufficient antecedent basis for this limitation in the claims. Claim 10, from which these claims depend, does not contain a limitation "a capture probe".

C) Claim 25 recites the limitation "discrete sites" in line 1. There is insufficient antecedent basis for this limitation in the claim. Claim 10, from which this claim depends, does not contain a limitation "discrete sites".

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary

skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. Claims 1-4, 6-10, 12-17 and 22-27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Navot et al. (U.S. Patent No. 6,335,165 B1) and Walt et al. (U.S. Patent No. 6,327,410 B1).

A) Navot et al. teaches a method of sequencing GC-rich regions of nucleic acids, the method comprising contacting modified GC-rich nucleic acid with a sequencing primer, synthesizing a complementary strand in a stepwise manner, in which an identity of each incorporated nucleotide is determined, and determining the sequence of the GC-rich nucleic acid (col. 7, lines 10-29; col. 12, lines 34-46). The nucleotide addition is catalyzed by a DNA polymerase (the first enzyme) (col. 14, lines 46-67).

The identity of each incorporated oligonucleotide can be determined by monitoring a release of a pyrophosphate (PPi) group and the detection of PPi is achieved enzymatically. The PPi formed in the sequencing reaction is converted to ATP by ATP sulfurylase (second enzyme) and the ATP production is monitored by the firefly luciferase (third enzyme) (col. 7, lines 60-67; col. 4, lines 55-67; col. 5, lines 1-36; col. 12, lines 66-67; col. 13, lines 1-35).

Another way of determining the identity of an incorporated nucleotide is achieved by using nucleotide analogs, which include a removable blocking group at the 3'-OH position and a removable reporter group. Following the addition of a nucleotide to the complementary strand the blocking group is removed to permit the addition of the next nucleotide. The removable reporter group allows identification of the incorporated nucleotide (col. 13, lines 43-67).

The target nucleic acid can be bound to a solid support either directly or indirectly, for example, through a capture probe (col. 10, lines 29-33). In another embodiment, either the sequencing primer or the target can be immobilized on beads (col. 15, lines 1-14).

B) Navot et al. do not teach microspheres (beads) randomly distributed on a surface of a substrate, where the substrate comprises discrete sites, and the discrete sites are wells. They do not teach the substrate being a fiber optic bundle.

Navot et al. teach a kit comprising amplification primers and a DNA polymerase (col. 6, lines 63-67; col. 7, lines 1-10; col. 9, lines 5-7).

C) Walt et al. teach microsphere-based analytical chemistry system in which the microspheres are distributed on a substrate which might be a fiber optic bundle (Abstract). The surface of the substrate comprises discrete sites into which at least two subpopulations of microspheres are distributed. Each of the microspheres comprises a bioactive agent and an optical signature which allows identification of the bioactive agent. The beads can be randomly distributed on the array (col. 3, lines 35-45; col. 4, lines 35-58). The bioactive agent attached to the microsphere can be a nucleic acid, particularly a nucleic acid probe (col. 8, lines 15-19; col. 9, lines 41-67; col. 10, lines 1-47). The array can be used for sequencing (col. 24, lines 51-52).

The substrate materials include glass, plastics and a variety of other materials. The surface of the substrate contains discrete sites, which might be wells, and the substrate may be a fiber optic bundle (col. 5, lines 32-46, lines 61-67; col. 6, lines 22-41).

Walt et al also teach a composition comprising a substrate with discrete sites (wells) and a population of microspheres randomly distributed in the wells, the microspheres comprising a bioactive agent (claims 1, 5, 9, 27 and 39).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have used microspheres randomly distributed on a substrate of Walt et al. as the beads in the pyrosequencing method of Navot et al. The motivation to do so, expressly provided by Walt et al., would have been that synthesis of nucleic acids was separated from their placement on the array and random distribution of beads was fast and inexpensive.

9. Claims 5 and 11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Navot et al. and Walt et al. as applied to claims 1 and 10 above, and further in view of Balch (U.S. Patent No. 6,083,763).

A) Claim 5 is drawn to the hybridization complexes comprising target sequences, sequencing primers, adapter probes and capture probes covalently attached to the microspheres. Claim 11 is drawn to a hybridization complex comprising capture probe, adapter probe and a target sequence.

B) Neither Navot et al. nor Walt et al. teach adapter probes.

C) Balch teaches molecular analysis aparatus for high-throughput analysis of molecular targets in complex mixtures. This apparatus can be used for DNA amplification and sequencing in an array format. (Abstract, Example III). Each location of the array comprises a capture probe attached to a solid substrate (col. 17, lines 28-41; col. 18, lines 55-66). The target probes (adapter probes) are designed to be complementary to both the capture probes and the target nucleic acids (col. 20, lines 39-49; Fig. 5a). The capture probes can be used directly to form hybridization complexes with the target nucleic acid sequences (col. 21, lines 21-23).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have used the adapter probes of Balch for the formation of primer-target complexes in

the combined method of Navot et al. and Walt et al. The motivation to do so, expressly provided by Balch, would have been that adapter probes a delivered unique binding domain for each site on an array.

10. Claims 18-21 and 28-30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Navot et al. and Walt et al. as applied to claims 1 and 10 above, and further in view of Nyren et al. (WO 98/13523).

A) Claims 18-21 are drawn to a kit for nucleic acid sequencing comprising a substrate with discrete sites, population of microspheres randomly distributed in these sites, the microsphres comprising capture probes, an extension enzyme, dNTPs, a second enzyme for conversion of PPi to ATP, a third enzyme for the detection of ATP, and dNTPs with different labels.

B) Navot et al. teaches a kit as described above, but does not teach a substrate with discrete sites, population of microspheres randomly distributed in these sites, the microsphres comprising capture probes, dNTPs, a second enzyme for conversion of PPi to ATP, a third enzyme for the detection of ATP, and dNTPs with different labels. Walt et al also teach a composition comprising a substrate with discrete sites (wells) and a population of microspheres randomly distributed in the wells, the microspheres comprising a bioactive agent (claims 1, 5, 9, 27 and 39), but does not teach dNTPs, a second enzyme for conversion of PPi to ATP, a third enzyme for the detection of ATP, and dNTPs with different labels.

C) Nyren et al. teach a kit comprising a sequencing primer, a polymerase, a detection enzyme means for identifying pyrophosphate release, dNTPs or ddNTPs (page 20, second paragraph; page 21, first paragraph).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have added kits of Nyren et al. to a kit and a composition disclosed by Navot et al. and Walt et al. The motivation to do so would have been that kits were conventional in the field of molecular biology and provided the benefits of convenience and cost-effectiveness for practitioners in the art.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Teresa E Strzelecka whose telephone number is (703) 306-5877. The examiner can normally be reached on M-F (8:30-5:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached at (703) 308-1119. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

May 1, 2003

Teresa Strzelecka, Ph. D.

Patent Examiner

Teresa Strzelecka

05/01/03